Journal of Pioneering Medical Sciences
Received: May 05, 2025 | Accepted: September 24, 2025 | Published: November 05, 2025
Volume 14, Issue 10, Pages 174-179

DOI https://doi.org/10.47310/jpms2025141024

Redox Homeostasis and Antioxidant Dysregulation in Chronic Myeloid Leukemia: Biomarker Potential for Disease Progression and TKI Response

Hiba Al-Nayyar[1*] and Kamel Ben-Mahrez[2]

[1,2]Biochemistry and Biotechnology Laboratory LR01ES05, Faculty of Sciences of Tunis, University of Tunis El Manar, El Manar II, Tunis 2092, Tunisia

*Corresponding author: Hiba Al-Nayyar (e-mail: hiba.alnayyar@fst.utm.tn).

©2025 the Author(s). This is an open access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0

Abstract **Background:** The BCR-ABL fusion gene drives chronic Myeloid Leukemia (CML), resulting in an oncoprotein with excessive tyrosine kinase activity that promotes abnormal cell growth. Treatments with tyrosine kinase inhibitors (TKIs) induce oxidative stress, but resistance can develop due to compromised antioxidant defenses. Reactive oxygen species (ROS) play a dual role; low levels support cell signaling, while high levels cause damage. The body counters ROS through antioxidants enzymes. In cancer, malignant cells adapt by managing oxidative stress, influencing therapy response. **Objectives:** The present study aimed to investigate redox homeostasis and antioxidant defense regulation in patients with chronic myeloid leukemia (CML) by measuring the levels of catalase (CAT), superoxide dismutase (SOD), glutathione (GSH), and reactive oxygen species (ROS) in three groups of patients receiving different tyrosine kinase inhibitor (TKI) therapies, and compared them with newly diagnosed CML cases and healthy controls. Furthermore, we sought to assess the potential of these redox markers as biomarkers for disease progression and therapeutic response. **Methods:** Blood samples of 120 CML patients (20 newly diagnosed and 100 on TKI) and 60 healthy controls were analyzed via ELISA. **Results:** results showed a significant oncogene's redox-disrupting effects in CML patients characterized by decreased levels of (CAT, SOD, GSH) and increased ROS versus controls (all $p<0.001$). TKI treatment improved most markers ($p<0.05$) except GSH. **Conclusions:** These findings highlight the potential of antioxidant enzymes and ROS as biomarkers of disease progression and treatment response in CML, and support the relevance of redox homeostasis in therapeutic monitoring.

Key Words CML; Oxidative stress; Antioxidants; Redox Homeostasis; biomarkers.

INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by the balanced reciprocal translocation t(9;22)(q34;q11), resulting in the formation of the BCR-ABL fusion gene. This genetic aberration leads to the production of the p210 BCR-ABL oncoprotein, which exhibits constitutive tyrosine kinase activity and dysregulates multiple signaling pathways involved in cell proliferation and apoptosis suppressor [1]. Tyrosine kinase inhibitors (TKIs), a cornerstone of CML therapy, exert their therapeutic effects partly by inducing oxidative stress. The extent of oxidative stress determines whether pro-apoptotic or pro-survival pathways are activated in leukemic cells[2]. Moreover, reactive oxygen species (ROS)-mediated genomic instability contributes to apoptotic signaling. Research indicates that oxidative stress contributes to tyrosine kinase inhibitor (TKI) resistance through both BCR-ABL-dependent and independent pathways, as chronic myeloid leukemia (CML) patients often show significantly reduced antioxidant defenses. An optimal oxidative balance is thus critical for effective TKI response [3]. Reactive oxygen species (ROS) are pivotal in various physiological and pathological processes. Their role in biological systems is dichotomous: at low to moderate levels, they function as redox signaling molecules essential for normal cellular physiology, a condition referred to as eustress[4]. Conversely, excessive ROS accumulation overwhelms antioxidant defenses, leading to oxidative stress, a state marked by molecular damage to proteins, lipids, and DNA[5]. The primary antioxidant defense system comprises enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), which

collectively neutralize superoxide radicals ($O_2 \cdot^-$) and hydrogen peroxide (H_2O_2)[6]. This antioxidant system serves an indispensable function in catalyzing the dismutation of superoxide radicals ($O_2 \cdot^-$) and hydrogen peroxide (H_2O_2). Superoxide dismutase (SOD)-mediated elimination of $O_2 \cdot^-$ not only prevents formation of the highly reactive peroxynitrite ($ONOO^-$) via the reaction ($O_2 \cdot^- + NO \cdot \rightarrow ONOO^-$), but also preserves physiological concentrations of nitric oxide ($NO \cdot$), a crucial signaling molecule involved in neurotransmission, vascular tone regulation, and inflammatory responses[7]. In cancer biology, redox imbalance and oxidative stress are central to tumorigenesis, progression, and therapeutic response [8]. However, certain malignancies undergo redox resetting, adapting to elevated ROS levels by upregulating antioxidant defenses. This adaptive mechanism fosters resistance to anticancer therapies via enhanced drug efflux, metabolic reprogramming, mutations in drug targets, activation of survival pathways, and impaired apoptotic signaling [9]. Elucidating these resistance mechanisms may provide novel therapeutic avenues to enhance treatment efficacy [10]. The present study aimed to evaluate oxidative stress and antioxidant defence regulation in patients with CML through the measurement of CAT, SOD, GSH, and ROS, as well as to assess their relevance as biomarkers in relation to disease progression and TKI treatment response.

METHODS

This research was approved by the Institutional Review Board of The National Center of Hematology, Mustansiriyah University (Baghdad, Iraq) with the approval number (nch-erc-p-23-1) on (22-10-2023). Informed consent was obtained from all subjects involved in the study.

Subjects

Study Population: This case control study included 120 CML patients (male and female, aged 18-60 years) whose blood samples were collected between January and October 2024 from three medical centers in Baghdad: Oncology Teaching Hospital, Baghdad Medical City, and the National Center of Hematology at Mustansiriyah University. The study comprised: 20 newly diagnosed CML patients (8 males, 12 females; age range: 30-58 years), with diagnoses confirmed by consultant physicians. 100 TKI-treated patients in the chronic phase of CML: 60 on Imatinib mesylate (Glivec®), 40 on Nilotinib (Tasigna®) and Bosutinib (Bosulif®).

Inclusion Criteria

The study enrolled both newly diagnosed CML patients and individuals receiving treatment with different tyrosine kinase inhibitors. Eligible participants were aged 18 to 60 years and all were in the chronic phase of CML, confirmed as Philadelphia chromosome-positive with BCR::ABL1 fusion verified by RT-PCR.

Exclusion Criteria

Patients younger than 18 or older than 60 years, pregnant or lactating women, and those with active systemic infections were excluded as well as individuals who were current smokers, using antioxidant supplements, or diagnosed with other genetic disorders or chronic illnesses.

Methods

Evaluation of Catalase (CAT), superoxide dismutase (SOD), Glutathione (GSH) and Reactive Oxygen Species (ROS) Levels in Blood Serum

The levels of CAT, SOD, GSH and ROS in the serum of CML patients and the control group were measured using a quantified using commercially available ELISA kits (Ylaboint/China).

Assay Procedure

Standard solutions were prepared as per kit instructions (YL boint/China). Blank wells received chromogen solutions and stop solution; standard wells contained 50 µL standard and 50 µL streptavidin-HRP; sample wells had 40 µL sample, 10 µL Labeled antibodies, and 50 µL streptavidin-HRP. The plate was incubated at 37°C for 60 minutes, washed five times, and developed with chromogen solutions A and B for 10 minutes in the dark. The reaction was stopped, and the absorbance at 450 nm was measured within 10 minutes. The concentration of the antioxidants (CAT and SOD), GSH, and ROS were calculated using a standard curve generated with ELISA reader (Bio Tech /USA). All samples were analyzed in duplicate to ensure accuracy and reproducibility.

RESULTS AND DISCUSSION

This study was conducted on 120 patients with CML; 20 patients were newly diagnosed and before the starting treatment regime, while the rest 100 patients were previously diagnosed and under treatment, 60 of them were treated with imatinib, and the other were treated either with nilotinib (20 patients) or Bosutinib (20 patients). All patients in chronic phase of CML.

The mean age of the patient group was 45.4±10.4 years, while the control group had a mean age of 41.2 ±9.2 years. The difference in age between the two groups was not statistically significant, as indicated by a p-value of 0.091. In terms of sex distribution, the patient group consisted of 64 males and 56 females, whereas the control group included 34 males and 26 females, (Table 1).

Study of antioxidants and reactive oxygen species between study groups

The group statistics comparing CML patients and controls across various biochemical parameters are presented in table 3. All assessed clinical biomarkers demonstrated statistically significant intergroup variation ($p<0.05$). CAT activity was reduced in patients (39.6±25.7) versus controls (55.4±12.2), also with a p-value of 0.001. SOD levels were markedly lower in patients (28.6±19.6) compared to controls (64.7±24.1), with a p-value of 0.001. ROS levels were

Table 1: Age and sex CML Patients and Controls at Study Enrollment.

Parameters	Group	N	Mean±SD†		p-value
Age	Patients	120	45.4±10.4		0.091
	Controls	60	41.2±9.2		
Sex	Patients	120	Male	64	0.893
			Female	56	
	Controls	60	Male	34	
			Female	26	

†Standard deviation

Table 2: Comparison of Selected biochemical markers Between CML Patients and Controls

Parameters	Group	N	Mean± SD	P-value
CAT (U/L)	Patients	120	39.6±25.7	0.001
	Controls	60	55.4±12.2	
SOD (U/L)	Patients	120	28.6±19.6	0.001
	Controls	60	64.7±24.1	
ROS (U/L)	Patients	120	379.6±284.7	0.001
	Controls	60	197.1±60.6	
GSH (U/L)	Patients	120	49.3±18.1	0.001
	Controls	60	90.3±18.2	

Table 3: Comparison of Selected Study Parameters between CML Patients groups and Controls.

Parameters	CML groups	N	Mean± SD†	P-value
CAT (U/L)	Newly diagnosis	20	23.8±6.4	*0.002
	Treated patients	100	42.4±27.0	**0.001
	Controls	60	55.4±12.2	
SOD (U/L)	Newly diagnosis	20	16.0±5.8	*0.001
	Treated patients	100	31.2±20.0	**0.001
	Controls	60	64.7±24.1	
ROS (U/L)	Newly diagnosis	20	802.0±2934	*0.001
	Treated patients	100	315.5±202.0	**0.001
	Controls	60	197.1±60.6	
GSH(U/L)	Newly diagnosis	20	48.6±17.2	*0.96
	Treated patients	100	48.8±16.9	**0.001
	Controls	60	90.3±18.2	

*Comparison between New diagnosis CML and Treated CML patients, ** Comparison among CML groups (New diagnosis, Treated) and Control group, †Standard deviation

significantly higher in patients (379.6±284.7) than in controls (197.1±60.6), with a p-value of 0.001. Lastly, GSH levels were lower in patients (49.3±18.1) compared to controls (90.3±18.2), with a p-value of 0.001. These findings indicate significant oxidative stress and reduced antioxidant capacity in patients compared to controls. The comparison of selected study parameters between (CML) patient groups and controls is detailed in table 4. The study included newly diagnosed CML patients (n=20), treated CML patients (n=100), and controls (n=30). CAT activity was also reduced in newly diagnosed patients (23.8±6.4) compared to treated patients (42.4±27.0) and controls (55.4±12.2), with p-values of 0.002 and 0.001, respectively. SOD levels were markedly lower in newly diagnosed patients (16.0±5.8) compared to treated patients (31.2±20.0) and controls (64.7±24.1), with p-values of 0.001 for both comparisons. ROS levels were significantly higher in newly diagnosed patients (802.0±2934) compared to treated patients (315.5±202.0) and controls (197.1±60.6), with p-values of 0.001 for both comparisons. Glutathione (GSH) levels did not show a significant difference between newly diagnosed (48.6±17.2) and treated patients (48.8±16.9) with a p-value of 0.96, but both groups had significantly lower levels compared to controls (90.3±18.2), with a p-value of 0.001. These findings highlight the differences in oxidative stress and antioxidant capacity across the CML patient groups and controls, emphasizing the impact of treatment on these parameters.

The group statistics comparing newly diagnosed CML patients with those treated with different tyrosine kinase inhibitors (TKIs) are presented in table 5. The study included newly diagnosed patients (n=20) and patients treated with Bosutinib (n=20), Nilotinib (n=20), and Imatinib (n=60). CAT activity was also reduced in newly diagnosed patients (23.8±6.4) compared to those treated with Bosutinib (38.1±26.6), Nilotinib (41.0±22.0), and Imatinib (44.9±28.8), with a p-value of 0.015. SOD levels were markedly lower in newly diagnosed patients (16.0±5.8) compared to those treated with Bosutinib (31.3±21.2), Nilotinib (33.12±25.7), and Imatinib (30.9±18.7), with a p-value of 0.014. Reactive oxygen species (ROS) levels were significantly higher in newly diagnosed patients (802.0±2934) compared to those treated with Bosutinib (248.5±111.7), Nilotinib (424.0±262.7), and Imatinib (301.2±191), with a p-value of 0.001. GSH levels did not show a significant difference between newly diagnosed patients (48.6±17.2) and those treated with Bosutinib (54.3±21.4), Nilotinib (42.1±15.2), and Imatinib (49.2±17.3), with a p-value of 0.207. These findings indicate that treatment with TKIs significantly improves oxidative stress markers and antioxidant capacity compared to newly diagnosed CML patients.

Correlation Between Study Parameters

The Pearson correlation coefficients among various variables are presented in the table 6, The table presents correlation analyses among oxidative stress markers (CAT, SOD, ROS and GSH). SOD ($r = 0.220$, $p = 0.028$) and GSH ($r = 0.264$, $p = 0.014$), while exhibiting a negative correlation with ROS ($r = -0.264$, $p = 0.015$). CAT demonstrated a strong positive correlation with SOD ($r = 0.773$, $p<0.001$) but negative correlations with ROS ($r = -0.227$, $p = 0.023$) and GSH ($r = 0.206$, $p = 0.04$). SOD was positively associated with GSH ($r = 0.298$, $p = 0.003$), while ROS inversely correlated with GSH ($r = -0.297$, $p = 0.003$). These results suggest interplay between antioxidants enzymes (CAT and SOD) regulation, glutathione and oxidative stress with ROS emerging as a critical factor.

DISCUSSION

The current study found a significant increase in CAT levels in contrast to the CML groups. The newly diagnosed CML patients displayed reduced CAT levels relative to treated individuals, though no substantial differences were noted among those receiving different tyrosine kinase inhibitors. Our findings align with the observations of Eras *et al.*, who reported significantly lower catalase (CAT) enzyme levels in leukemia patients101.79 ±70.15 U/ml compared to healthy individuals 143.75 ±105.81 U/ml [11]. Our findings are consistent with the work of Arsalan *et al.*, who similarly observed no statistically significant differences in CAT levels between CML patient groups treated with Nilotinib versus Imatinib [2].

The present research demonstrated reduced SOD enzyme level in both newly diagnosed and treated CML patients compared to the control group, while no significant differences were observed among patients receiving different TKI treatments. SOD and other antioxidant enzymes play a critical role in scavenging free radicals and protecting cells from oxidative stress. Numerous studies have demonstrated altered SOD enzyme profile in cancer cells compared to the normal control cells [12, 13]. These results are consistent with previous studies demonstrating significantly reduced SOD levels in CML patients compared to healthy control groups [6, 14] versus other Multiple investigations have reported dysregulation of antioxidant enzyme systems across various biological compartments in leukemia patients, including serum, leukocytes, and erythrocytes [15,16]. The relative stability of H_2O_2 enables its diffusion across cellular membranes, potentially reaching critical sites such as nuclear DNA. This oxidative burden may explain the observed depletion of superoxide radicals ($O2•–$) and consequent compensatory elevation of SOD activity [17]. The current study revealed no statistically significant differences in SOD concentrations among CML patients treated with various TKIs. This observation is consistent with existing literatures that found minimal disparity in SOD expression between treatment-sensitive and treatment-resistant cases [3,18].

Our finding in this study showed that there are significant differences in level of GSH between CML patients and control groups while there is no significant difference in the level of GSH between newly diagnosed CML patients and treated patients, as well as there is no significant difference in

Table 4: Comparison of Selected Study Parameters between CML Patient Groups and Controls

Parameters	CML groups	N	Mean± SD†	P-value
CAT (U/L)	Newly diagnosis	20	23.8±6.4	0.015
	Bosutinib	20	38.1±26.6	
	Nilotinib	20	41.0±22.0	
	Imatinib	60	44.9±28.8	
SOD (U/L)	Newly diagnosis	20	16.0±5.8	0.014
	Bosutinib	20	31.3±21.2	
	Nilotinib	20	33.12±25.7	
	Imatinib	60	30.9±18.7	
ROS (U/L)	Newly diagnosis	20	802.0±2934	0.001
	Bosutinib	20	248.5±111.7	
	Nilotinib	20	424.0±262.7	
	Imatinib	60	301.2±191	
GSH (U/L)	Newly diagnosis	20	48.6±17.2	0.207
	Bosutinib	20	54.3±21.4	
	Nilotinib	20	42.1±15.2	
	Imatinib	60	49.2±17.3	

†Standard deviation

Table 6: Pearson Correlation Coefficients among Variables

Variables		CAT	SOD	ROS	GSH
CAT	R	-	0.773**	-0.227	0.206
	P-value		0.001**	0.023*	0.04*
SOD	R	0.773**	-	0.149	0.298
	P-value	0.001**		0.172	0.003**
ROS	R	-0.227	0.149	-	-0.297
	P-value	0.023*	0.172		0.003**
GSH	R	0.206	0.298	-0.297	-
	P-value	0.04*	0.003**	0.003**	

the level of GSH among CML patients treated with different TKIs. The ratio of GSH to GSSG can be used as a measure of oxidative stress in cells [18]. Our results are aligned with the previous study, which showed the predominant cellular antioxidant, GSH, is essential for preserving redox balance within cells. Numerous redox-modulating enzymes, such as thiol reductases, peroxiredctases and peroxidases, are functionally dependent on GSH availability. Thus, interventions designed to reduce GSH, quail ability could markedly impact cell survival and therapeutic response by shifting the redox state of the cells [19]. Other studies that are compatible with current study, which showed that markedly, reduce the GSH level in CML patients in comparison with healthy looking people; GPX enzyme reduces the H_2O_2 and the organic peroxides while oxidizing the GSH. The oxidized glutathione, GSSG, is reduced back to GSH by the glutathione reductase enzyme (GRx) in NADPH presence [18,20].

Glutathione (GSH), the most abundant non-enzymatic reactive oxygen species (ROS) scavenger, along with its associated enzymatic systems, glutathione reductase (GR), glutathione peroxidase (GPX), and glutathione S-transferase (GST), plays a pivotal role in hydrogen peroxide (H_2O_2) detoxification and regulates key cellular processes, including proliferation, division, and differentiation. Dysregulation of GSH metabolism has been implicated in various malignancies, particularly hematological cancers [21].

Our study found that ROS levels were significantly higher in CML patients compared to healthy controls. Additionally, newly diagnosed CML patients had increased ROS levels relative to those treated with tyrosine TKIs. Further analysis among CML patient groups revealed that newly diagnosed individuals exhibited the highest ROS levels.

The present study's correlation analysis demonstrated important relationships between markers CAT, SOD, GSH and ROS in CML cases. Our findings showed that CAT strongly correlated with SOD and negatively with ROS and GSH. SOD was positively linked to GSH, while ROS inversely correlated with GSH, suggesting that ROS plays a key role in the interplay between antioxidants activity and CML progression. The antioxidant enzymes CAT and SOD function within the same biological pathway, collectively mitigating oxidative stress by catalyzing the conversion of hydrogen peroxide (H_2O_2) into water and oxygen.

BCR-ABL1-positive cells exhibited elevated ROS generation, with differential ROS levels observed between Imatinib-sensitive and Imatinib-resistant cells. Imatinib induced greater DNA damage in drug-sensitive cells. Additionally, Imatinib-susceptible cells displayed a more pronounced reduction in GSH content and GPX activity upon treatment. In contrast, Imatinib-resistant cells demonstrated heightened catalase activity and a decline in MMP. These findings indicate that BCR-ABL1 kinase disrupts ROS homeostasis, and Imatinib resistance is associated with altered GPX and CAT activity, as well as MMP dysregulation [18]. These findings support the conclusion that redox signaling and oxidative stress play pivotal roles in cancer biology, influencing tumor initiation, progression, and therapeutic responsiveness [8].

CONCLUSIONS

The study demonstrates significant oxidative stress dysregulation in CML patients, characterized by markedly reduced antioxidant enzymes levels (CAT and SOD), and glutathione (GSH) alongside elevated ROS compared to healthy controls (all $p<0.001$). Treatment with TKIs partially restored redox homeostasis, with treated patients showing significantly higher CAT ($p=0.015$), SOD ($p=0.014$) and lower ROS ($p<0.001$) than newly diagnosed cases, though GSH levels remained persistently low across all patient groups. These findings highlight antioxidant enzymes and ROS may serve as key biomarkers of CML progression and treatment response in CML, and support the significance of redox balance in therapeutic monitoring.

Acknowledgement

We would like to acknowledge all the people who provided the blood samples and the staff of the National Center of Hematology, Mustansiriyah University, Baghdad, Iraq, for their support and the facilities they provided for sample collection.

Conflicts of Interest

The authors declare no conflicts of interest.

Ethical Statement

This research was approved by the Institutional Review Board of The National Center of Hematology, Mustansiriyah University (Baghdad, Iraq) with the approval number (nch-erc-p-23-1) on (22-10-2023).

REFERENCES

[1] Siegel, R.L., *et al. Cancer Statistics, 2025. CA: A Cancer Journal for Clinicians*, vol. 75, 2025, pp. 10–45.

[2] Arsalan, H.M., *et al*. "Prospective Biochemical Analysis of Chronic Myeloid Leukemia Patients in Response to Tyrosine Kinase Inhibitors." *Pakistan Journal of Zoology*, vol. 55, 2023, pp. 2103–2111.

[3] Allegra, A., *et al*. "Oxidative Stress and Chronic Myeloid Leukemia: A Balance between ROS-Mediated Pro- and Anti-Apoptotic Effects of Tyrosine Kinase Inhibitors." *Antioxidants*, vol. 13, 2024, p. 461.

[4] Azzi, A. "Oxidative Stress: What Is It? Can It Be Measured? Where Is It Located? Can It Be Good or Bad? Can It Be Prevented? Can It Be Cured?" *Antioxidants (Basel, Switzerland)*, vol. 11, 2022, pp. 1431–1442.

[5] Sies, H. "Oxidative Eustress: The Physiological Role of Oxidants." *Science China Life Sciences*, vol. 66, 2023, pp. 1947–1948.

[6] Chyad, Z.S., and A.D. Matter Al-Maliki. "Investigation and Assessment of Oxidant–Antioxidant Status of Some Enzymes and Vitamins in Iraqi Patients with Chronic Myeloid Leukemia." *Current Issues in Pharmacy and Medical Sciences*, vol. 37, 2024, pp. 162–165.

[7] Jomova, K., *et al*. "Several Lines of Antioxidant Defense against Oxidative Stress: Antioxidant Enzymes, Nanomaterials with Multiple Enzyme-Mimicking Activities, and Low-Molecular-Weight Antioxidants." *Free Radical Biology and Medicine*, vol. 98, 2024, pp. 1323–1367.

[8] Cabrera-Serrano, A.J., *et al*. "Crosstalk Between Autophagy and Oxidative Stress in Hematological Malignancies: Mechanisms, Implications, and Therapeutic Potential." *Antioxidants (Basel, Switzerland)*, vol. 14, 2025, pp. 264–315.

[9] Forman, *et al*. "An Overview of Mechanisms of Redox Signaling." *Journal of Molecular and Cellular Cardiology*, vol. 73, 2014, pp. 2–9.

[10] Hegedűs, C., *et al*. "Redox Control of Cancer Cell Destruction." *Redox Biology*, vol. 16, 2018, pp. 59–74.

[11] Eras, N., *et al*. "An Investigation of the Relation Between Catalase C262T Gene Polymorphism and Catalase Enzyme Activity in Leukemia Patients." *Archives of Medical Science: AMS*, vol. 17, 2021, pp. 928–933.

[12] Ahmad, R., *et al*. "Leukocyte Superoxide Dismutase Activity in Patients with Chronic Myeloid Leukemia." *Revista Brasileira de Hematologia e Hemoterapia*, vol. 34, 2012, pp. 394–395.

[13] Valko, M., *et al*. "Free Radicals and Antioxidants in Normal Physiological Functions and Human Disease." *The International Journal of Biochemistry & Cell Biology*, vol. 39, 2007, pp. 44–84.

[14] Dikic, D., *et al*. "Inflammation Promotes Oxidative and Nitrosative Stress in Chronic Myelogenous Leukemia." *Biomolecules*, vol. 12, 2022.

[15] Naz, A., *et al*. "Oxidative Stress and Total Antioxidant Status in Acute Leukemia at Diagnosis and Post Remission Induction Phase." *Pakistan Journal of Pharmaceutical Sciences*, vol. 26, 2013, pp. 1123–1130.

[16] Bakan, N., *et al*. "Glutathione Peroxidase, Glutathione Reductase, Cu-Zn Superoxide Dismutase Activities, Glutathione, Nitric Oxide, and Malondialdehyde Concentrations in Serum of Patients with Chronic Lymphocytic Leukemia." *Clinica Chimica Acta: International Journal of Clinical Chemistry*, vol. 338, 2003, pp. 143–149.

[17] Zuo, X.L., *et al*. "Levels of Selenium, Zinc, Copper, and Antioxidant Enzyme Activity in Patients with Leukemia." *Biological Trace Element Research*, vol. 114, 2006, pp. 41–53.

[18] Ammar, M., *et al*. "Relationship of Oxidative Stress in the Resistance to Imatinib in Tunisian Patients with Chronic Myeloid Leukemia: A Retrospective Study." *Journal of Clinical Laboratory Analysis*, vol. 34, 2020, e23050.

[19] Chowdhury, A.A., *et al*. "Synergistic Apoptosis of CML Cells by Buthionine Sulfoximine and Hydroxychavicol Correlates with Activation of AIF and GSH-ROS-JNK-ERK-iNOS Pathway." *PLOS ONE*, vol. 8, 2013, e73672.

[20] Polat, M.F., *et al*. "Oxidant/Antioxidant Status in Blood of Patients with Malignant Breast Tumour and Benign Breast Disease." *Cell Biochemistry and Function*, vol. 20, 2002, pp. 327–331.

[21] Trombetti, S., *et al*. "Oxidative Stress and ROS-Mediated Signaling in Leukemia: Novel Promising Perspectives to Eradicate Chemoresistant Cells in Myeloid Leukemia." *International Journal of Molecular Sciences*, vol. 22, 2021.